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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Weaning Outcomes in Patients with Brain Injury

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Abstract

Background: Despite the need for specific weaning strategies in neurological patients, evidence is generally insufficient or lacking. We aimed to describe the evolution over time of weaning and extubation practices in patients with acute brain injury compared with patients who are mechanically ventilated (MV) due to other reasons.

Methods: We performed a secondary analysis of three prospective, observational, multicenter international studies conducted in 2004, 2010, and 2016 in adults who had need of invasive MV for more than 12 h. We collected data on baseline characteristics, variables related to management ventilator settings, and complications while patients were ventilated or until day 28.

Results: Among the 20,929 patients enrolled, we included 12,618 (60%) who started the weaning from MV, of whom 1722 (14%) were patients with acute brain injury. In the acutely brain-injured cohort, 538 patients (31%) did not undergo planned extubation, defined as the need for a tracheostomy without an attempt of extubation, accidental extubation, and death. Among the 1184 planned extubated patients with acute brain injury, 202 required reintubation (17%). Patients with acute brain injury had a higher odds for unplanned extubation (odds ratio [OR] 1.35, confidence interval for 95% [CI 95%] 1.19–1.54; $p < 0.001$), a higher odds of failure after the first attempt of weaning (spontaneous breathing trial or gradual reduction of ventilatory support; OR 1.14 [CI 95% 1.01–1.30; $p = 0.03$]), and a higher odds for reintubation (OR 1.41 [CI 95% 1.20–1.66; $p < 0.001$]) than patients without brain injury. Patients with hemorrhagic stroke had the highest odds for unplanned extubation (OR 1.47 [CI 95% 1.22–1.77; $p < 0.001$]), of failed extubation after the first attempt of weaning (OR 1.28 [CI 95% 1.06–1.55; $p = 0.009$]), and for reintubation (OR 1.49 [CI 95% 1.17–1.88; $p < 0.001$]). In relation to weaning evolution over time in patients with acute brain injury, the risk for unplanned extubation showed a downward trend; the risk for reintubation was not associated to time; and there was a significant increase in the percentage of patients who underwent extubation after the first attempt of weaning from MV.

Conclusions: Patients with acute brain injury, compared with patients without brain injury, present higher odds of undergoing unplanned extubated after weaning was started, lower odds of being extubated after the first attempt, and a higher risk of reintubation.

Keywords: Mechanical ventilation, Outcome, Brain injury, Weaning, Extubation

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Introduction

Neurologic-related respiratory failure from severe central nervous system dysfunction is one of the most frequent reasons for initiating invasive mechanical ventilation (MV) [1]. Critical care of patients with acute brain injury primarily focuses on the management of intracranial pressure, optimization of cerebral blood flow, and avoidance of secondary brain injury through the prevention of hypercarbia, hypoxemia, and hypotension [2]. Patients with brain injury are traditionally ventilated with high tidal volumes and low positive end-expiratory pressure levels, due to concerns of permissive hypercapnia and high positive end-expiratory pressure on intracranial pressure and cerebral blood flow [3, 4]. However, high tidal volume and driving pressure have been identified as potential risk factors for acute lung injury and worsening of respiratory function in patients with acute brain injury [3, 5, 6]. In addition, patients with acute brain injury are characterized by challenging or delayed weaning process due to the high extubation failure rate and poor level of consciousness [7–9]. Although some clinical practice recommendations have been published to guide the respiratory support and the weaning process of MV in patients with acute brain injury, evidence is generally insufficient or lacking [10–15]. Recent data suggest the importance of the need for specific extubation and weaning strategies in the neurocritical care population [7, 8, 10, 13].

Therefore, the main objective of this study was to describe and compare baseline characteristics, weaning and extubation practices, and associated outcomes among neurologic patients with different types of brain injury (hemorrhagic stroke, ischemic stroke, or brain trauma) and between patients with acute brain injury who are MV and nonneurologic, MV patients. A secondary objective was to explore the evolution over time of weaning and extubation practices in these groups of patients.

Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines for observational cohort studies [16]. The protocol was approved by the research ethics board of each participating institution (Comité Ético de Investigación Clínica del Hospital Universitario de Getafe, Spain, with approval number A03/16), and the need for informed consent was obtained according to local rules. We conducted three prospective, observational, multicenter international studies, in 2004 [17], 2010 [18], and 2016 [1], in all adults who needed invasive MV for more than 12 h, which included a total of 1262 intensive care units (ICUs) from 45 countries. We followed the same methodology for all studies. For the purpose of the present study, we performed a secondary analysis of three cohorts. In all studies, we collected data on baseline characteristics (age, sex, and severity at admission estimated by Simplifed Acute Physiology Score II, which ranges from 0 [lower severity] to 163 [higher severity], daily gas exchange, variables related to management ventilator settings, sedation, neuromuscular blockers, and complications [acute respiratory distress syndrome, sepsis, ventilator-associated pneumonia]). These data were collected daily while patients were ventilated or until day 28. The Glasgow Coma Scale (GCS) was assessed at ICU admission and daily in the absence of sedative drugs. Patients were followed until discharge from hospital. In the event of discharge from hospital before day 28 after starting MV, the status on this day was registered. National coordinators recruited local investigators from eligible ICUs (see full list of investigators in the supplementary material). Only the research team members at each site were aware of the purpose and the precise timing of the study.

For this analysis, we classified patients as primary patients with acute brain injury if they had a primary structural neurologic disease (cerebrovascular accident of ischemic stroke, hemorrhagic stroke, which included intracerebral hemorrhage and subarachnoid hemorrhage, and brain trauma with or without multisystem trauma) as the reason for initiation of MV. Patients with a depressed level of consciousness as a result of other neurological issues, metabolic abnormalities, or intoxication and/or overdose were excluded. We also excluded patients who were transferred to another hospital before starting the weaning process and patients who did not meet the criteria for initiating weaning (Table E1 in the Supplemental Material). For comparison, we used a control group of patients who were ventilated for nonneurologic reasons. We explored weaning and extubation practices. The onset of weaning was the time that the physician in charge considered the patient was likely to resume and sustain spontaneous breathing after they met standard criteria for weaning readiness. Weaning was performed by either a reduction in the level of ventilator support or a trial of spontaneous breathing. Patients who fulfilled weaning criteria and tolerated a weaning attempt without signs of distress and followed by extubation were considered planned extubated. Those who could not be considered planned extubated were due to the following reasons: accidental extubation, need for a tracheostomy or presence of a previous tracheostomy, and death during the weaning process. These were considered unplanned extubation. We defined failure of weaning attempt as the failure to pass a trial by objective indices, such as tachypnoea, tachycardia, hypertension, hypotension, hypoxemia or acidosis, and arrhythmia, and subjective indices, such as agitation or distress, depressed

Table 1 Baseline characteristics and evolution over time between patients without brain injury and categories of patients with brain injury

Patients' characteristics and evolution	Nonneurologic[a] (*n* = 10,896)	Hemorrhagic stroke (*n* = 712)	Ischemic stroke (*n* = 331)	Brain trauma (*n* = 679)	*p* value
Year of study, *n* (%)					0.008
2004	2573 (24)	156 (22)	71 (21)	162 (24)	
2010	4388 (40)	296 (41)	139 (42)	227 (33)	
2016	3935 (36)	260 (36)	121 (36)	290 (43)	
Age, mean (SD) (yr)	61 (17)	60 (15)	66 (14)	46 (20)	< 0.001
Female sex, *n* (%)	4076 (37)	338 (47)	123 (37)	161 (24)	< 0.001
SAPS II, mean (SD), (points)	42 (18)	44 (15)	45 (16)	41 (16)	< 0.001
Complications during mechanical ventilation, *n* (%)					
ARDS	577 (5)	15 (2)	3 (1)	14 (2)	< 0.001
VAP	298 (3)	36 (5)	8 (2)	40 (6)	< 0.001
Sepsis	1544 (14)	54 (7.5)	20 (6)	53 (8)	< 0.001
Cardiovascular failure	4152 (38)	192 (27)	73 (22)	323 (33)	< 0.001
Renal failure	1942 (18)	57 (8)	26 (8)	36 (5)	< 0.001
Hepatic failure	450 (4)	13 (2)	2 (1)	9 (1)	< 0.001
Hematological failure	840 (8)	18 (2.5)	6 (2)	21 (3)	< 0.001
Days with GCS lower than 10 points, median (25th–75th percentiles)	0 (0–2)	2 (0–6)	2 (0–5)	2 (0–6)	< 0.001
Sedation, n (%)	8792 (81)	543 (76)	210 (63)	574 (84)	< 0.001
Days, median (25th–75th percentiles)	3 (2–5)	3 (2–6)	2 (1–4)	4 (2–7)	< 0.001
Neuromuscular blocking, n (%)	1198 (11)	61 (8.5)	18 (5)	77 (11)	0.001
Days, median (25th–75th percentiles)	2 (1–3)	1 (1–3.5)	1 (1–2)	2 (1–4.5)	0.157
Days of mechanical ventilation until start weaning, median (25th–75th percentiles)	4 (2–8)	6 (3–11)	5 (3–10)	6 (3–11)	< 0.001
GCS at start weaning, median (25th–75th percentiles) (points)	11 (10–11)	9 (6–11)	10 (6–11)	10 (7–11)	0.001
Ratio PaO_2/FiO_2 at start weaning, mean (SD)	272 (93)	303 (88)	293 (91)	293 (95)	0.519
$PaCO_2$ at start weaning, mean (SD) (mm Hg)	40 (9)	37 (7)	38 (8)	37 (7)	< 0.001
ICU mortality, *n* (%)	1099 (11)	85 (12)	39 (12)	57 (8)	0.117

ARDS, acute respiratory distress syndrome, COPD, chronic pulmonary obstructive disease, FiO_2, fraction of inspired oxygen, GCS, Glasgow Coma Scale, ICU, intensive care unit, $PaCO_2$, partial pressure of carbon dioxide, PaO_2, partial pressure of oxygen, SAPS, Simplified Acute Physiology Score, SD, standard deviation, VAP, ventilator-associated pneumonia

[a] Nonneurological cohort includes patients with following reasons for mechanical ventilation: COPD (649), asthma (153), other chronic pulmonary disease (166), ARDS (380), postoperative respiratory failure (3762), cardiac failure (696), aspiration (354), pneumonia (1242), sepsis (1095), trauma (737), cardiac arrest (699), other acute respiratory failure (780), and neuromuscular disease (180)

mental status, diaphoresis, and evidence of increasing effort. We defined failed extubation as the need for reintubation within 48 h following extubation. The following weaning-related variables were recorded: the method for first weaning attempt (spontaneous breathing trial [SBT] [T-tube, low pressure support {PS}, continuous positive airway pressure, or other modes] or gradual reduction of ventilatory support, defined as a progressive decrease of ventilator support to a level that allows extubation [PS, synchronized intermittent mandatory ventilation with or without PS, or other modes]), failure in first weaning attempt, method of disconnection in patients failing the first attempt (SBT [T-tube, low PS, continuous positive airway pressure, or other modes] or gradual reduction of ventilatory support [PS, synchronized intermittent mandatory ventilation with or without PS, or other modes]), date of extubation, need for reintubation and postreintubation tracheostomy. Patients were followed until discharge from the hospital.

Statistical Analysis

Continuous variables were expressed as means (standard deviations) or medians (25th–75th percentiles), and qualitative variables were expressed as numbers and percentages. Continuous variables were compared by using Student's *t* test or the Mann–Whitney *U* test according to their distribution, and categorical variables were compared by using the χ^2 test or the Fischer's exact test, as

appropriate. The objectives of the analysis were to investigate the association between acute brain injury and two main outcomes: unplanned extubation and failure of extubation, defined as the need for reintubation, in planned extubated patients. We performed two logistic multivariate models. In the first model, the following variables were included: acute brain injury (no/yes), age, sex, simplified acute physiology score II, complications during MV (acute respiratory distress syndrome, associated ventilator pneumonia, sepsis, cardiovascular failure, acute renal failure, hepatic failure, and hematologic failure), days with a GCS score lower than 10 points, days of MV until starting weaning, arterial blood gases on the last day before starting weaning (partial pressure of carbon dioxide [$PaCO_2$], ratio partial pressure of oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2]), sedation, and neuromuscular blocking during the time of MV. In the second model, the following variables were included: acute brain injury (no or yes), age, sex, simplified acute physiology score II, days of MV until starting weaning, days until extubation, arterial blood gases on the last day before starting weaning ($PaCO_2$, ratio PaO_2-to-FiO_2), sedation, and neuromuscular blocking during the time of MV, the method for weaning (SBT or gradual reduction support), and failure in the first attempt of weaning. The same models were performed in patients with acute brain injury to estimate the differences between hemorrhagic stroke, ischemic stroke, and brain trauma. The effect of time was evaluated by performing a multivariate model in which the interaction term was added and tested for significance. To evaluate the changes more thoroughly, a stratification by year of study was performed. All missing data were multiply imputed through the multivariate imputation by chained equations procedure. Incomplete dichotomous variables were imputed by using a logistic regression model, whereas linear regression was used to impute incomplete continuous variables. We generated 10 imputed data sets. Interactions were tested before performing the multivariate logistic regression. A two-tailed p value of less than 0.05 was considered to indicate statistical significance. We used STATA 16.0 (College Station, TX), for all the analyses.

Results

Patients

During the study periods, 2929 patients were eligible for inclusion; among these, 12,618 patients who started the process of weaning were selected for the analysis (Fig. E1 in the supplemental material). From this cohort, 1722 patients (14%) were classified as patients with acute brain injury: 712 patients presented with hemorrhagic stroke, 331 patients presented with ischemic stroke, and 679 patients presented with brain trauma. Baseline characteristics and evolution with time between patients without brain injury and different subgroups of patients with acute brain injury are presented in Table 1. We reported the rate of missing data for the following variables: GCS (14%), ratio of PaO_2-to-FiO_2 (44%), and $PaCO_2$ at the start of weaning (40%). Characteristics of excluded patients are shown in Table E1 in the supplemental material.

Unplanned Extubation

From included cohort, 2743 patients (22%) did not undergo a planned extubation for different reasons: 623 patients due to accidental extubation during the weaning period, 1874 patients due to tracheotomy during the weaning process or presence of a previous tracheostomy, and 246 patients who died during this period (Table E2 in the supplemental material). In patients with acute brain injury and patients without brain injury, the main reason for not undergoing planned extubation was the need for a tracheostomy without an attempt of extubation (79% of patients with acute brain injury and 65% of patients without brain injury).

The comparison between patients who started weaning with no planned extubation or planned extubation is shown in Table 2. After adjusted analysis, patients with acute brain injury had a higher odds of undergoing an unplanned extubation after beginning weaning: odds ratio (OR) 1.35 (confidence interval for 95% [CI 95%] 1.19–1.54; $p < 0.001$). The odds for unplanned extubation after start weaning is maintained over time, although with a downward trend: OR 1.88 (CI 95% 1.43–2.46; $p < 0.001$) in 2004; 1.27 (CI 95% 1.04–1.54; $p = 0.018$) in 2010; and 1.21 (CI 95% 0.98–1.48; $p = 0.066$). A change is mainly observed between 2004 and 2010, so the odds decreased by 32%. The odds remained constant from 2010 to 2016, decreasing by approximately 4%.

In the group of patients with acute brain injury, patients with hemorrhagic stroke had a higher odds for unplanned extubation after start weaning: OR 1.47 (CI 95% 1.22–1.77; $p < 0.001$) versus 1.40 (CI 95% 1.07–1.82; $p = 0.012$) in ischemic stroke versus 1.22 (CI 95% 1.00–1.48; $p = 0.046$) in patients with brain trauma in comparison with nonneurologic patients. The odds for unplanned extubation after start weaning has decreased over time mainly from 2004 to 2010. In patients with hemorrhagic stroke, the OR in 2004 was 2.99 (CI 95% 1.90–4.69; $p < 0.001$); in 2010, the OR was 1.42 (CI 95% 1.04–1.94; $p = 0.024$); and in 2016, the OR was 1.36 (CI 95% 1.02–1.82; $p = 0.037$). In brain trauma, the evolution was as follows: in 2004, OR 2.59 (CI 95% 1.61–4.18; $p < 0.001$); in 2010, OR 1.14 (CI 95% 0.79–1.64; $p = 0.478$); and in 2016, OR 1.13 (CI 95% 0.84–1.52; $p = 0.399$). In patients

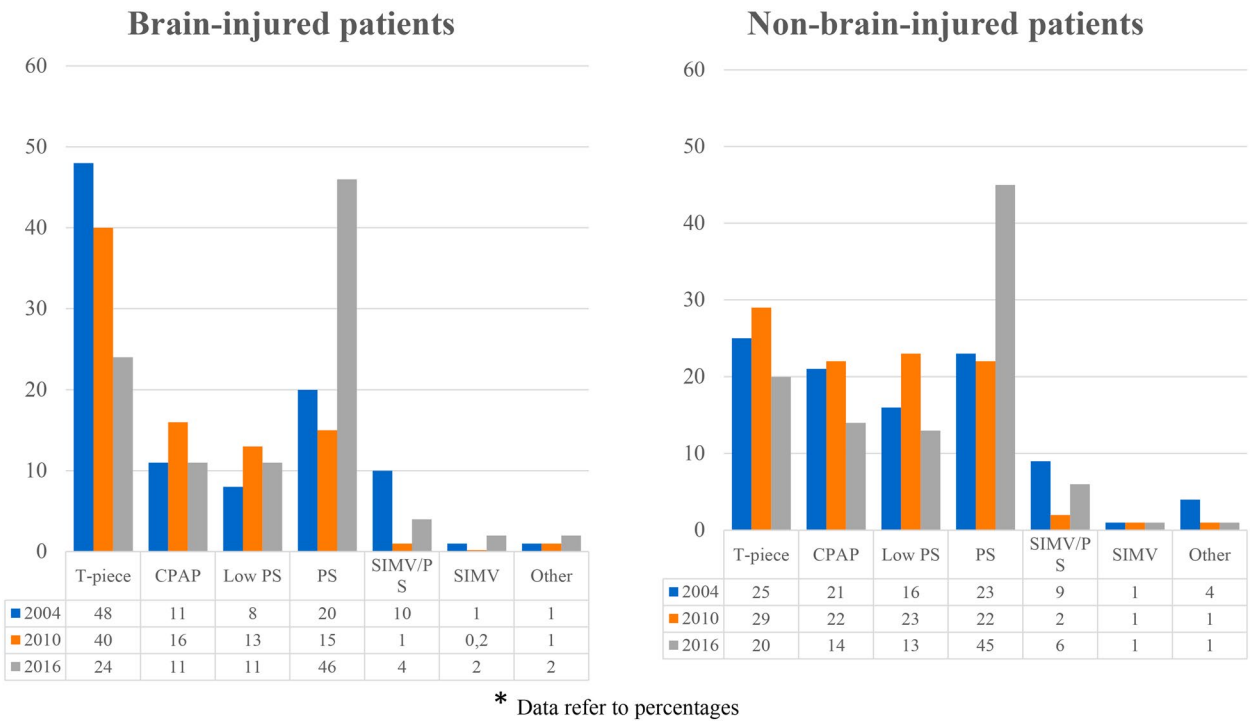

Fig. 1 Evolution over time of method used for the first attempt of weaning in patients with brain injury and patients without brain injury. CPAP, continuous positive airway pressure, PS, pressure support, SIMV, synchronized intermittent mandatory ventilation

with ischemic stroke, there was no significant influence probably because of the small sample size: in 2004, OR 1.45 (CI 95% 0.67–3.11; $p=0.339$); in 2010, OR 1.53 (CI 95% 1.01–2.33; $p=0.043$) and in 2016, OR 1.35 (CI 95% 0.89–2.04; $p=0.149$).

Planned Extubation and Weaning Outcomes

Among the 9875 planned extubated patients, 1320 patients required reintubation (13%). Median time to reintubation was 19 h (interquartile range 4–57 h) in patients with acute brain injury versus 30 h (12–71 h) in patients without brain injury ($p=0.003$). Table 3 shows the comparison between reintubated and non-reintubated patients. After being adjusted for confounders variables, patients with acute brain injury had a higher probability for reintubation: OR 1.41 (CI 95% 1.20–1.66; $p<0.001$). There was no interaction associated with time ($p=0.653$). In the group of patients with acute brain injury, there were differences in the odds for reintubation: OR 1.49 (CI 95% 1.17–1.88; $p<0.001$) in hemorrhagic stroke; 1.43 (CI 95% 1.02–2.01; $p=0.036$) in ischemic stroke and 1.32 (CI 95% 1.02–1.71; $p=0.031$) in brain trauma. There was also no effect of time.

Table 4 shows the comparison of evolution in weaning outcomes over time in planned extubated patients. From the first study, we noticed a significant increase in the percentage of patients who underwent extubation after the first attempt of weaning: 54% in 2004, 61% in 2010, and 71% in 2016 ($p<0.001$). Patients with acute brain injury had a lower odds of undergoing extubation after the first attempt of weaning than patients without brain injury: OR 1.14 (CI 95% 1.01–1.30; $p=0.03$). Within the acutely brain-injured cohort, patients with hemorrhagic stroke had a higher odds of undergoing a failed extubation: OR 1.28 (CI 95% 1.06–1.55; $p=0.009$).

Methods of Weaning Over Time

Figure 1 shows the evolution over time in the methods used for the first attempt of weaning. In patients with acute brain injury and patients without brain injury, a gradual reduction of ventilator support, mainly PS, has become the main method for weaning from MV. It is noteworthy that in 2004 and 2010 the main method for the first disconnection attempt was a spontaneous breathing test, whereas in 2016 slightly more than half of the patients were weaned with PS progressively decreasing and without a spontaneous breathing test. A similar finding was observed in the methods used for weaning in patients who failed the first attempt (Fig. 2). Changes in the method of weaning in each category of acute brain injury are shown in Fig. E2 in the supplemental material.

Table 2 Comparison between patients who initiated weaning and were extubated on a planned basis and patients who did not have a planned extubation

Patients' characteristics and evolution	Weaning and unplanned extubation[a] ($n=2743$)	Weaning and planned extubation ($n=9875$)	p value
Year of study, *n* (%)			< 0.001
2004	444 (16)	2518 (25)	
2010	1303 (47)	3747 (38)	
2016	996 (36)	3610 (36.5)	
Age, mean (SD) (yr)	59 (17)	60 (17)	0.995
Female sex, *n* (%)	937 (34)	3761 (38)	< 0.001
SAPS II, mean (SD) (points)	44 (17)	42 (17)	< 0.001
Neurological disease, *n* (%)			< 0.001
No	2205 (80)	8691 (88)	
Hemorrhagic stroke	234 (8.5)	478 (5)	
Ischemic stroke	99 (4)	232 (2)	
Brain trauma	205 (7)	474 (5)	
Complications during mechanical ventilation, *n* (%)			
ARDS	188 (6.5)	421 (4)	< 0.001
VAP	164 (6)	218 (2)	< 0.001
Sepsis	499 (18)	1172 (12)	< 0.001
Cardiovascular failure	1169 (43)	3471 (35)	< 0.001
Renal failure	532 (19)	1529 (15)	< 0.001
Hepatic failure	107 (4)	367 (4)	0.655
Hematological failure	210 (8)	675 (7)	0.137
Days with GCS lower than 10 points, median (25th–75th percentiles)	1 (0–6)	0 (0–2)	< 0.001
Sedation, *n* (%)	2179 (79)	7940 (80)	0.267
Days, median (25th–75th percentiles)	5 (2–9)	2 (1–5)	< 0.001
Neuromuscular blocking, *n* (%)	401 (15)	953 (10)	< 0.001
Days, median (25th–75th percentiles)	2 (1–4)	1 (1–2)	< 0.001
Days of mechanical ventilation until start weaning, median (25th–75th percentiles)	9 (5–15)	4 (2–7)	< 0.001
GCS at start weaning, median (25th–75th percentiles) (points)	11 (7–11)	11 (10–11)	< 0.001
Ratio PaO_2-to-FiO_2 at start weaning, mean (SD)	253 (89)	278 (93)	0.103
$PaCO_2$ at start weaning, mean (SD) (mm Hg)	41 (9)	39 (8)	< 0.001
ICU mortality, *n* (%)	401 (15)	879 (9)	< 0.001

ARDS, acute respiratory distress syndrome, COPD, chronic pulmonary obstructive disease, FiO_2, fraction of inspired oxygen, GCS, Glasgow Coma Scale, ICU, intensive care unit, $PaCO_2$, partial pressure of carbon dioxide, PaO_2, partial pressure of oxygen, SAPS, Simplified Acute Physiology Score, SD, standard deviation, VAP, ventilator associated pneumonia

[a] Reasons for unplanned extubation were as follows: accidental extubation during the weaning period (623 patients), tracheotomy during the weaning process or to have a previous tracheostomy (1874 patients), or exitus (246 patients)

Discussion

This multicenter, prospective, observational study showed that, compared with nonneurologic patients requiring MV, those with brain injury (1) had a higher odds of undergoing unplanned extubation after weaning was started; (2) had a lower odds of undergoing extubation after the first attempt; and (3) showed a higher odds for reintubation. Concerning weaning evolution over time in patients with acute brain injury, the odds for unplanned extubation after beginning weaning showed a downward trend over time; the odds for reintubation was not associated with time; and there was a significant increase in the percentage of patients who underwent extubation after the first attempt of weaning. Further, a gradual reduction of PS was the principal method of weaning in patients with acute brain injury and patients without brain injury.

The weaning process is a fundamental component of the management of all patients receiving MV; however, until recently, there have been little data regarding specific extubation and weaning management of patients with brain injury [7, 8, 10, 14, 15]. Because the

Table 3 Comparison between non-reintubated and reintubated patients

Patients' characteristics and evolution	Non-reintubated ($n = 8555$)	Reintubated ($n = 1320$)	*p* value
Year of study, *n* (%)			< 0.001
2004	2252 (26)	266 (20)	
2010	3286 (38)	461 (35)	
2016	3017 (35)	593 (45)	
Age, mean (SD) (yr)	60 (17)	63 (17)	< 0.001
Female sex, *n* (%)	3268 (38)	493 (37)	0.563
SAPS II, mean (SD) (points)	41 (17)	45 (17)	< 0.001
Neurological disease, *n* (%)			0.001
No	7573 (88.5)	1118 (85)	
Hemorrhagic stroke	388 (4.5)	90 (7)	
Ischemic stroke	194 (2)	38 (3)	
Brain trauma	400 (5)	74 (6)	
Complications during mechanical ventilation, *n* (%)			
ARDS	329 (4)	92 (7)	< 0.001
VAP	159 (2)	59 (4)	< 0.001
Sepsis	957 (11)	215 (16)	< 0.001
Cardiovascular failure	2908 (34)	563 (43)	< 0.001
Renal failure	1262 (15)	267 (20)	< 0.001
Hepatic failure	310 (4)	57 (4)	0.211
Hematological failure	569 (7)	106 (8)	0.069
Days with GCS lower than 10 points, median (25th–75th percentiles)	0 (0–2)	0 (0–3)	< 0.001
Sedation, *n* (%)	6891 (81)	1049 (79)	0.352
Days, median (25th–75th percentiles)	2 (1, 4)	4 (2, 6)	< 0.001
Neuromuscular blocking, *n* (%)	808 (9)	145 (11)	0.080
Days, median (25th–75th percentiles)	1 (1–2)	1 (1–3)	0.842
Days of mechanical ventilation until start weaning, median (25th–75th percentiles)	4 (2–7)	5 (3–9)	< 0.001
GCS at start weaning, median (25th–75th percentiles) (points)	11 (10–11)	11 (9–11)	0.002
Ratio PaO_2/FiO_2 at start weaning, mean (SD)	280 (93)	265 (90)	< 0.001
$PaCO_2$ at start weaning, mean (SD) (mm Hg)	39 (9)	40 (9)	0.052
Failure of first attempt of withdrawal mechanical ventilation, *n* (%)	3139 (37)	506 (38)	0.257
Days of weaning, median (25th–75th percentiles)	1 (1–2)	1 (1–2)	0.100
Noninvasive positive pressure ventilation post extubation, *n* (%)	852 (10)	362 (27)	< 0.001
ICU mortality, *n* (%)	504 (6)	375 (28)	< 0.001

ARDS, acute respiratory distress syndrome, COPD, chronic pulmonary obstructive disease, FiO_2, fraction of inspired oxygen, GCS, Glasgow Coma Scale, ICU, intensive care unit, $PaCO_2$, partial pressure of carbon dioxide, PaO_2, partial pressure of oxygen, SAPS, Simplified Acute Physiology Score, SD, standard deviation, VAP, ventilator-associated pneumonia

application of MV is associated with serious complications and costs [19], it is essential to shorten the duration of ventilation as much as possible [20, 21]. In the general population, some authors have reported increased mortality for each additional day without a weaning success after the first attempt to withdraw MV [22]. By contrast, some others [23] found higher mortality only for weaning lasting more than 7 days. In the present study, patients with acute brain injury had a higher risk of not being planned extubated after start weaning, and ventilation days until start weaning and ICU mortality were higher in nonplanned extubated patients than in planned extubated patients. The main reason for not being planned extubated was the performance of a tracheotomy without an attempt of extubation, and patients with acute brain injury experienced a higher rate of tracheostomy compared with patients without brain injury. Features associated with the increased need for tracheostomy in patients with acute brain injury were probably related to low levels of arousal and secretion clearance [24]. The risk for unplanned extubation after beginning weaning was maintained over time with a decreasing trend, mainly

Table 4 Comparison of temporal evolution of weaning outcomes in planned extubated patients

Weaning outcomes	Nonneurologic (*n* = 8691)	Hemorrhagic stroke (*n* = 478)	Ischemic stroke (*n* = 232)	Brain trauma (*n* = 474)	*p* value
Proportion of patients extubated at first attempt, *n* (%)					< 0.001
2004	1233 (52)	50 (38)	32 (49)	56 (41)	
2010	2351 (57)	122 (49)	61 (49.5)	103 (54.5)	
2016	2688 (69)	162 (63)	85 (70)	207 (71)	
Days for weaning in patients who failed first attempt, median (25th–75th percentiles)					< 0.001
2004	3 (2–4)	3 (2–5)	2.5 (2–3)	3 (2–5)	
2010	3 (2–5)	4 (2–8)	3 (2–6)	6 (2–11)	
2016	3 (2–4)	3 (2–5)	3 (2–5)	3 (2–6)	
Reintubation, *n* (%)					< 0.001
2004	230 (10)	14 (12.5)	12 (20)	10 (9)	
2010	401 (12)	28 (15)	15 (17)	17 (11)	
2016	487 (16)	48 (26)	11 (13)	47 (22)	
Tracheotomy in reintubated patients, *n* (%)					< 0.001
2004	74 (32)	8 (57)	5 (42)	5 (50)	
2010	147 (37)	14 (50)	13 (50)	12 (87)	
2016	205 (42)	39 (81)	6 (54)	34 (72)	

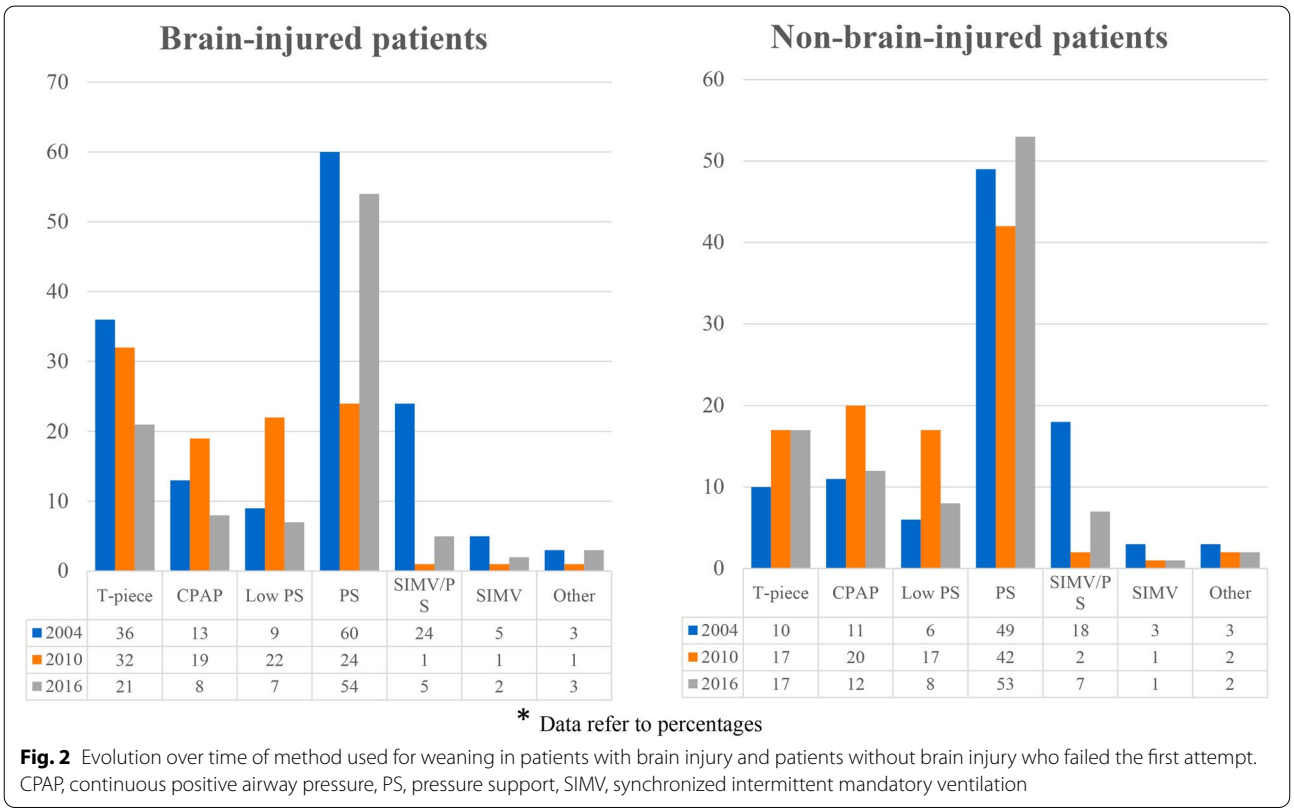

Fig. 2 Evolution over time of method used for weaning in patients with brain injury and patients without brain injury who failed the first attempt. CPAP, continuous positive airway pressure, PS, pressure support, SIMV, synchronized intermittent mandatory ventilation

between 2004 and 2010, so the risk decreased by 32% but remained relatively constant from 2010 to 2016. On the other hand, we found a significant increase over time in the percentage of patients who underwent extubation after the first attempt of weaning. This could be due to an increased experience in the ability to correctly select

those patients able to maintain airway patency, as the risk of reintubation has not changed over time. However, patients with acute brain injury had a lower probability of being extubated after the first attempt than patients without brain injury. Obtaining a sustained adequate mental status may be a reason for delaying extubation in patients with acute brain injury.

Extubation failure can also impair outcomes and is associated with a longer length of ventilation and a longer length of stay in the ICU and the hospital and can it worsen survival [19, 25]. In contrast with the evidence that patients with acute brain injury are especially prone to extubation failure, with high reintubation rates [7, 26], our group found comparable reintubation rates after planned extubation between patients with acute brain injury and patients without brain injury in a previous study [3]. In the present study, however, there was a slight increase in the rate of reintubation in patients with acute brain injury, which may be due to a lower GCS on the last day of MV before the start of weaning. In several studies [7–9] specifically looking for predictors of extubation failure in neurocritical care patients, a low GCS has been repeatedly identified as a risk factor for reintubation. Although some literature exists to assess indicators for extubation readiness and predictors of extubation failure in patients with acute brain injury, there is still a substantial lack of evidence about the process of discontinuation from the ventilator. A future large, prospective, observational study will be conducted to describe current practices of weaning, focusing on decisions on the timing of extubation and tracheostomy in patients with severe brain injury, providing a validated predictive score of successful extubation [27].

A gradual reduction of ventilatory support was the principal method of weaning in our cohort of patients with acute brain injury and patients without brain injury. As patients improved in the condition for which MV was required, the physician may prefer to progressively decrease ventilator support to a level that allows extubation. This common practice could explain the present finding, but it may not allow drawing a clear boundary between ventilatory support and weaning. So, the differences observed in the proportion of extubated patients after the first disconnection attempt could be motivated by this fact. According to this idea, most patients were receiving PS ventilation mode before an initial SBT or direct extubation in a recent multinational, observational study of invasive MV discontinuation [28]. Likewise, there was a significant increase over time in the use of PS as the main mode of ventilatory support in other analyses of four international observational studies of our group [1]. On the other hand, a notable variation in MV weaning practices has been reported in another international study in which, of the included patients, 22.7% underwent direct extubation, 49.8% underwent an initial SBT, and 8.0% underwent a direct tracheostomy [29]. A significant variation in ventilator modes of weaning has also been identified in other studies [22, 28] such as direct extubation without any SBT, T-piece, or low PS SBT. A meta-analysis found that T-piece SBTs were the optimal method for evaluating weaning readiness [30], whereas another meta-analysis showed that PS resulted in higher rates of successful extubation than T-piece SBTs [31]. Another study found the same rate of successful extubation with or without using an SBT in a mixed medical and surgical population of patients [26]. None of these studies specifically refer to patients with acute brain injury. American Thoracic Society guidelines for weaning stated moderate-quality evidence to recommend PS SBTs, without any specific recommendation in patients with brain injury [32].

Our study has several limitations. First, this was a post hoc analysis of previously and prospectively collected clinical data from a wide variety of ICUs, patient conditions, and clinical practices. In addition, the large number of ICUs participating may cause heterogeneity in patients' management and treatment. We have not assessed the intercountry variability in MV weaning practices that have recently been observed in several international studies [1, 29]. Second, the onset of weaning was defined as the first attempt at separating the patient from the ventilator and it started when the physician in charge considered the patient likely to resume and sustain spontaneous breathing, but we could not confirm if they met the standard criteria for weaning readiness or if a possible gradual reduction of support may have occurred before. Third, no information was recorded on the implementation of sedation and weaning protocols [20, 21, 33, 34] nor the precise duration of spontaneous ventilation trials, which significantly influences the outcome of weaning [35–37]. However, the use of protocols for sedation and weaning was not associated with a higher rate of short weaning in the recent international observational study by Beduneau et al. [22]. Fourth, we could not analyze the impact of some complications such as ICU-acquired muscle weakness [38] or delirium [39] on the duration of weaning. Fifth, we did not collect details regarding the strategies applied for the treatment of intracranial hypertension or specific monitoring data (intracranial pressure, cerebral perfusion pressure, etc.), but we assume that patients with acute brain injury have been treated according to the most recent protocols and guidelines. Sixth, we have not been able to apply a recent classification of weaning according to the duration of disconnection of MV, the WIND (Weaning according to a New Definition) classification [22, 40], because

the design of the studies does not allow estimating the duration of weaning in patients with tracheostomy or reintubation, as these two scenarios were considered final events with no subsequent follow up. Finally, some extra-analysis may have improved the interpretability of the results such as a time-interrupted time-series analysis to explore the evolution of weaning and extubation strategies over time, and even analyze separately into two groups (no extubation attempted due to tracheostomy or death, and accidental extubation) those patients who did not undergo planned extubation. Additionally, the high rate of missingness for the following variables: GCS (14%), ratio PaO_2-to-FiO_2 at the start of weaning (44%), and $PaCO_2$ at the start of weaning (40%) may cause some bias in the results. In addition, failure to take into account correlation may lead to the regression estimates being less efficient.

Conclusions

According to pooled data from our cohort, patients with acute brain injury, compared with patients without brain injury, present a higher odds of unplanned extubation after weaning was started, a lower odds of extubation after the first attempt, and a higher risk of reintubation. The gradual reduction of PS was the main method of weaning in patients with acute brain injury and patients without brain injury.

Supplementary Information
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Conflicts of interest
The authors declare that they have no conflicts of interest.

Ethical Approval/Informed Consent
We confirm adherence to ethical guidelines and indicate ethical approvals (institutional review board) and use of informed consent.

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